**Title:** Comparative efficacy of 4 oral analgesics for the initial management of acute musculoskeletal extremity pain

**Investigators:** Andrew Chang, M.D; David Esses, M.D; E. John Gallagher, M.D.

**Objective:** To perform a randomized, double blind 4-arm clinical trial of the comparative efficacy of 4 oral analgesics in the initial management of acute musculoskeletalextremity pain presenting to the ED.

## Introduction

According to a recent study, over 44 million emergency department (ED) visits per year are for a chief complaint related to pain. Approximately 29%, or 12.8 million, of these visits result in a prescription for an analgesic.[1] Yet, there are only a handful of studies that compare the efficacy of acute pain management of the most commonly prescribed oral analgesics.[2-7]

The Cochrane Collaboration has produced several reviews describing the effectiveness of codeine, both with and without acetaminophen, as well as a review of the efficacy of oxycodone alone or in combination with acetaminophen. Indirect comparisons over a period of 4-6 hours demonstrated greater efficacy with oxycodone compared to codeine.[8-10]Most of the studies included in the reviews were postoperative dental studies utilizing extraction of the third molar as the pain model. There are no Cochrane reviews that describe the efficacy of hydrocodone.

Two randomized controlled trials were found comparing hydrocodone and codeine for chronic pain. Rodriguez et. al. found no significant difference in either analgesia or incidence of side effects in a study of 121 patients using 5 mg of hydrocodone vs. 30 mg of codeine, both in combination with 500 mg of acetaminophen.[11]Palangio et al. in a three armed study design with 469 patients, found greater analgesia in the 15/400 mg hydrocodone/ibuprofen group compared to the 60/600 mg of codeine/acetaminophen.[6]

We have conducted three randomized clinical trials of oral opioids for patients discharged from the ED following presentation for acute musculoskeletal pain. The first compared hydrocodone/acetaminophen against codeine/acetaminophen and found no difference in change in pain intensity when patients were contacted 24-hours post-discharge.[12] The second compared oxycodone/acetaminophen against codeine/acetaminophen and again found no difference at 24 hours (manuscript is in "revise and resubmit" status).The third trial compared oxycodone/acetaminophen against hydrocodone/acetaminophen and also failed to show a difference in pain control at 24 hours following ED discharge (preliminary and unpublished data). The design of these studies differed from other studies of oral analgesics in that patients were called 24 hours after they left the ED, and they were asked to recall their pain intensity just prior to their most recent dose of pain medication and again 2 hours after ingestion of the study medications.

An alternative to oral opioid analgesics combined with acetaminophen is the combination of non-steroidal antiinflammatory drugs (NSAIDS) and acetaminophen. A review published in 2010 found the combination of various NSAIDS and acetaminophen

to be superior to acetaminophen alone in 17 of 20 studies.[13]The combination of ibuprofen and acetaminophen published since that review has been found to be more effective than each drug alone in 4 out of 5 trials of patients following dental surgery.[14-17]Only one small ED study that examined the effect of the 800 mg ibuprofen/1000 mg acetaminophen combination on musculoskeletal pain one hour after administration did not find it to be superior to either of the component drugs.[18]

We could find only one direct comparison between an ibuprofen/acetaminophen combination and an oral opioid combination. Patients who received 400 mg ibuprofen/ 1000 acetaminophen following extraction of a third molar had significantly less pain and greater pain relief in the 12 hour period after analgesic administration than patients who received 30 mg codeine/1000 mg acetaminophen.[14]

For this proposed study, we wished to look at the comparative efficacy of a single dose of 4 oral analgesics given while the patient is still in the ED. We believe this will enhance our understanding of these commonly prescribed oral analgesics by eliminating recall bias,which may have played a role in driving our prior findings comparing acetaminophen/codeine vs. hydrocodone/acetaminophen and oxycodone/acetaminophen toward the null of no difference among the 3 combination analgesics when assessed 24 hours later.

**Methods**

Design:

This will be a randomized, double blind, comparative efficacy trial of oral analgesics with four single-dose treatment arms: oxycodone 5 mg/ acetaminophen 325

mg, hydrocodone 5mg/acetaminophen 300mg, codeine 30 mg/acetaminophen 300mg, and ibuprofen 400 mg/acetaminophen1000 mg.

Setting:

The study will be performed simultaneously in 2 teaching hospitalsED's affiliated with the Albert Einstein College of Medicine, both located in the Bronx, approximately 5 miles apart, with a total of 180,000 adult visits annually. Both EDsare staffed by trained bilingual (Spanish and English) salaried research associates (RAs) available 24 hours a day/7 days a week. The research associates receive training in the ethical and practical aspects of data collection and a practicum with a senior research associate. Some of the RAs have been enrolling study patients for 5-10 years.

Patients:

Inclusion criteria: Patients age 21 to 64 years of age; complaint of acute pain of less than seven days duration; location of pain in one or more extremities defined as distal to and including the shoulder joint in the upper extremities and distal to and including the hip joint in the lower extremities; radiologic evaluation is planned; and willingness to provide NRS pain scores after discharge from the ED.

Exclusion criteria: Inability to reach patient on patient's cell phone while in the ED; past use of methadone; chronic condition requiring frequent pain management such as sickle cell disease, fibromyalgia, or any neuropathy; history of an adverse reaction to any of the study medications; opioids taken in the past 24 hours; ibuprofen or acetaminophen taken in past 8 hours; pregnancy by either urine or serum HCG testing;

breastfeeding per patient report; history of peptic ulcer disease; report of any prior use of recreational narcotics; medical condition that might affect metabolism of opioid analgesics, acetaminophen, or ibuprofen such as hepatitis, renal insufficiency or failure, hypo- or hyperthyroidism, Addison's or Cushing's disease; taking any medicine that might interact with one of the study medications, such as antidepressant SSRI's or Tricyclics, antipsychotics, anti-malaria medications quinidine or halofantrine, Amiodarone or Dronedarone, diphenhydramine, celecoxib, ranitidine, cimetidine, ritanovir, terbinafine, or St John's Wort.

Measures

Pain intensity will be assessed by an 11-point numeric rating scale (NRS) where 0 indicates no pain, 10 indicates worst possible pain. The primary endpoint will be the difference between NRS pain between the time immediately prior to ingestion of the study medication and 2 hours later. Secondary outcomes include NRS scores at 1 hourpain based on a 4-point Likert scale (none, mild, moderate, severe), and overall satisfaction with the pain medication using a 4-point Likert scale: very satisfied, satisfied, unsatisfied, or very unsatisfied with the study medication. Other outcomes include the incidence of side effects (nausea, vomiting, itchiness, rash,drowsiness, or confusion).

Baseline information will be obtained from the patient including demographic characteristics and a listing of all over-the-counter, topical, and prescribed analgesics taken in the 24 hours prior to enrollment. Diagnosis, rescue medication, and any other treatment received will be recorded, such as application of ice and splints.

Protocol:

Patients will be referred to the study by the patient's provider. The treating attending will confirm that the patient has met enrollment criteria and assess whether the patient has capacity to provide informed consent. RAs will describe the study in detail and obtain informed consent. Following randomization all patients will have their pain scores assessed immediately before administration of the study drug and 1 hour later while in the ED. If the patient remains in the ED, additional NRS pain scores and incidence of side effects will be assessed at 2 hours post-baseline. Patients who are discharged prior to 2 hours will be called at the appropriate time to obtain their pain scores. Since radiologic imaging is required for study entry, it is anticipated that the majority of patients will have most of their pain scores assessed while still in the ED. In our 3 prior oral opioid studies, more than 95% of study subjects were reached by phone at 24 hours. Thus, we do not anticipate any difficulty in being able to contact patients up to 2 hours after study medication is administered.

An on-line random number generator (www.randomization.com) will be used to allocate patients in blocks of 8to one of four experimental groups: oxycodone 5mg/acetaminophen 325mg, hydrocodone 5mg/acetaminophen 300mg, codeine 30mg/acetaminophen 300mg, or ibuprofen 400mg/acetaminophen 1000 mg. The opioid and acetaminophen combinations were selected to reflect commonly used analgesics for musculoskeletal pain. The choice of dose for the ibuprofen/acetaminophen combination

is based on a recently published study performed in the ED[18]and our desire to not miss an analgesic effect by administering a sub-therapeutic dose.

The research pharmacist will ensure proper allocation concealment by inserting each study medication combination into 3 identical unmarked opaque gel capsules, filling any void with small quantities of lactose to equalize weight. The capsules will be placed in numbered packetsby the research pharmacist working in an area distant from and inaccessible to ED staff. Each packet will have a sealed opaque envelope stapled to it that indicates what medication it contains so that the assignment is readily available if this information is needed clinically due to a serious adverse reaction. The RAs will retrievethe packets in sequential order and the nurse will dispense the medication to the patient. Patients, providers, and RAs will be blinded to study allocation.

Patients who require rescue medications will receive oxycodone 5 mg (without acetaminophen). This will be determined subjectively (i.e. if the patient requests additional pain medication or the treating physician decides that additional pain medication is needed). Discharge medications will be administered by the treating physician as per his/her usual care.

Data Collection and Processing

Data will be collected on a standardized data collection instrument in REDCAP, an electronic data capture system. The PI will review the data collected and informed consent documentsweekly for accuracy and completeness.

Data analysis

The primary data analysis will be a one-way analysis of variance testing the null hypothesis that there are no differences between the effect of the medications on mean change in pain from baseline to 2 hours post-baseline with a significance level of 0.05. If there is evidence to reject the null hypothesis we will conduct the set of t-tests comparing all pairwise mean differences in pain. The Bonferroni method will be used to adjust the overall significance level of 0.05 in order to account for multiple comparisons. The data will be presented as the difference between each pair of means and the set of 95% simultaneous Bonferroni CIs around the differences. SPSS version 22 (Chicago, IL.) will be used to conduct all data analyses. Data will be stored in an identified format in the event that a metaanalysis of studies is performed in the future.

Sample Size Calculation

The following parameters were used to calculate the sample size: an overall 2-sided significance level of 0.05 (0.008 for each t-test using the Bonferroni correction), power of 80%, 1.3 NRS unit or greater difference in change in pain between groups based on a standard definition of the minimal clinically significant difference in pain, and a within group standard deviation of 2.6 based on estimates of variability of change in pain in response to oral opioid analgesics. Using these parameters 100 patients are needed in each group for a total of 400 patients. We will plan to continue to enroll patients until we have 400 patients with usable data (not missing primary outcome or other critical data points). Based on past experience we estimate not needing more than

20 additional subjects to order to reach our target sample size of 400 patients. We used nQuery Advisor 7.0 (Los Angeles, CA) to calculate the sample size.

Data safety and monitoring

Data monitoring committee and interim analysis.This committee will be composed of Dr. Polly Bijur, PhD, a statistician and epidemiologist, and Dr. Benjamin Friedman who will meet quarterly tomonitor adverse events, recruitment, and enrollmentAn interim analysis, which will be approved by the DSMC prior to randomization, will be conducted after 200 subjects (50 in each treatment arm) with analyzable data have been enrolled. The purpose of the interim analysis is to identify one or more treatments that are clearly inferior or superior to the others. A clinically important difference in change in pain has been defined as 2 units or more on an NRS scale or 20 mm or more on a VAS score. We will examine the point estimates of the change in pain. If one or more arms has a mean decrease in pain that is at least 2 NRS units less than in other arms, that arm(s) will be discontinued regardless of statistical significance. For example, if group A has mean pain scores that decrease from 8 NRS units to 4 NRS units over time, and group B has mean pain scores that decrease from 8 NRS units to 6 NRS units, we will discontinue treatment B. If one group is clearly superior by this much the trial will be terminated.

Conclusion

This randomized, double-blind clinical trial is expected to further our understanding of the relative efficacy of 4 commonly used oral analgesics for acute musculoskeletal extremity pain. In particular, we are interested in comparing the efficacy of high-dose ibuprofen/acetaminophen with traditional combinations of opioids and

acetaminophen. The results of these studies are intended to improve the emergency medicine physician's ability to manage acute extremity pain in the emergency department.

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